**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In the Matter of US Application No. 10/553,462

**DECLARATION OF DR MATTHEW ROSE**

I, Dr Matthew Rose, of Unipath Limited, Bedford United Kingdom, do hereby declare as follows:

1. I have read the specification of this application. It contains a written description of the invention as now claimed in full, clear, concise and exact terms as to enable any person skilled in the art to use the invention. In particular, a person skilled in the art would be able, based on the disclosure of the specification as originally filed, to identify that a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR) by determining that her ADMA level is greater than 1.5 μmol/L.

2. All of the statements concerning enablement made in the last response that was filed in connection with this application are true. In the interest of brevity, those statements will not be repeated here.

2. The key point in relation to enablement is that the invention requires determining that a pregnant woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR. In other words, as explained at page 3, lines 26 to 30 of the specification, the invention concerns identifying those women who are susceptible to pre-eclampsia or those fetuses that are susceptible to IUGR. Essentially, the invention is a "risk test". Women who display an ADMA level greater than 1.5 μmol/L at 4 to 25 weeks gestation will be placed in a high risk bracket and monitored further for any signs of pre-eclampsia or IUGR.

3. The invention does not, as the Examiner seems to be suggesting, require diagnosing pre-eclampsia or IUGR. In other words, the invention is not a "diagnostic test".

4. In this regard, an analogy can be drawn between the invention and predicting the risk of myocardial infarction. Several "risk tests" have been developed for myocardial infarction. For example, an elevated cholesterol level is a risk marker for myocardial infarction, as is smoking. Those patients that display an elevated cholesterol level and/or smoke are placed in a high risk bracket and monitored for any signs of myocardial infarction. However, not all smokers with an elevated cholesterol level suffer myocardial infarction. As a result, such markers cannot form the basis of a "diagnostic test".

5. The same is true for the invention. Those women identified as being at risk of developing pre-eclampsia in accordance with the invention will be monitored carefully for any appearance of the disease. However, not necessarily all of the women identified as being at risk will go on to develop pre-eclampsia.

6. The invention is important because it offers an initial stage risk test for pre-eclampsia and IUGR. Symptoms of pre-eclampsia and IUGR do not normally present until the latter half of pregnancy. By then, it is too late to take steps to try to avoid the complications associated with each disease. At present, women are identified as being at risk of developing pre-eclampsia or her fetus being at risk of IUGR using past history. In other words, those women who developed pre-eclampsia in a previous pregnancy are placed in a high risk bracket and monitored accordingly. However, this method cannot take account of first time mothers who are young and healthy. An early test that allows the risk of developing pre-eclampsia or IUGR to be determined in any pregnant woman or fetus, such as that provided by the invention, would represent a big stride forward in the field.

7. The invention now being claimed is based on the surprising finding that an ADMA level of greater than 1.5 μmol/L in a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation is indicative of the woman being <u>at risk of</u> developing pre-eclampsia or her fetus being <u>at risk of</u> developing IUGR. This finding is supported by sound experimental evidence in the Example of this application. Based on the

disclosure in the Example and elsewhere in the specification, a person skilled in the art is capable of carrying out the invention now being claimed. A person skilled in the art would not have to perform undue experimentation to make and use the invention.

8. I have read all the documents cited by the Examiner in support of the rejection of lack of enablement. I do not believe that any of them cast a doubt on the ability of a person skilled in the art to carry out the invention being claimed.

9. The Examiner concludes from various documents, such as Cooke *et al.*, Fard *et al.*, Hamasaki *et al.*, Kielstein *et al.* and Fang *et al.*, that an ADMA level of greater than 1.5 μmol/L could result from other disorders or conditions. Such disorders include cardiovascular disease, renal problems and diabetes. I agree. However, Fard, Hamasaki, and Kielstein do not discuss measuring the level of ADMA in pregnant woman, and therefore are not relevant to the enablement of the present claims. Further, the present claims are not directed to determining the underlying cause of an increased ADMA level, nor to diagnosing pre-eclampsia. The present claims are directed to determining that a woman is <u>at risk</u> of developing pre-eclampsia or her fetus is at risk of developing IUGR if the woman's plasma ADMA level is greater than 1.5 μmol/L. As discussed in the last response, pre-eclampsia is a complex, multifactorial disease, which involves changes in, amongst others, a woman's cardiovascular function, metabolic function and renal function. Hence, renal problems early in pregnancy, for instance, will contribute to the woman being diagnosed as having pre-eclampsia later in pregnancy. As a result, whatever the underlying cause of elevated ADMA, it can still be used as an indicator in early pregnancy that a pregnant woman is <u>at risk of</u> developing pre-eclampsia or her fetus is <u>at risk of</u> developing IUGR.

10. I have also read the documents by López-Jaramillo and Holden *et al.* All the studies disclosed in those two documents looked at ADMA levels in women with pre-eclampsia and those without pre-eclampsia and compared the levels. They did not look at the relationship of ADMA levels and risk of subsequent development of pre-

eclampsia. No conclusion can be drawn from these documents concerning the suitability of ADMA as a risk marker for pre-eclampsia. The Examiner is correct that the two documents appear to contradict each other concerning the level of ADMA later in pregnancy. However, this has no bearing on its suitability in early pregnancy to determine the risk of pregnant woman developing pre-eclampsia or her fetus developing IUGR.

11. Also, it is unreasonable to require that a risk marker show the same changes throughout the progression of the disease (in this case, pregnancy). Another putative risk marker for pre-eclampsia, PP13, does not show this behavior. PP13 levels start off lower in patients who subsequently develop pre-eclampsia compared with normal patients and then crosses-over the normal profile to end up higher in pre-eclamptic patients than in normal patients. Accordingly, the level of ADMA at the end of pregnancy has no bearing on its use early in pregnancy as a risk marker for pre-eclampsia or IUGR.

12. I therefore believe that the invention being claimed is enabled by the present specification.

13. In addition, Holden *et al.* does not disclose a method of the invention. As mentioned above, Holden and colleagues looked at ADMA levels in women with pre-eclampsia and those without pre-eclampsia and compared the levels. In other words, the women either had pre-eclampsia or did not. No conclusions were reached concerning the risk of women subsequently developing pre-eclampsia or their fetuses developing IUGR. Indeed, in studies such as the one disclosed in Holden *et al.*, control women are monitored throughout pregnancy and only included in the study if they do not develop pre-eclampsia at any stage. Holden also does not disclose or suggest measuring ADMA in a plasma sample taken from a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation to determine that the woman is at risk of developing pre-eclampsia. Further, Holden does not disclose determining that a woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of

ADMA is greater than 1.5 μmol/L in the woman. I therefore believe that the claimed invention is also novel.

14. Hence, in summary, I reiterate that the claimed invention represents an important tool in the prevention and management of pre-eclampsia and IUGR. An ADMA level of greater than 1.5 μmol/L in a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation is surprisingly indicative of a risk (not a certainty) that the woman will develop pre-eclampsia or her fetus will develop IUGR. A person skilled in the art would be able to carry out the claimed invention based on the information in the specification. The documents cited by the Examiner support this fact without disclosing the claimed invention. I therefore submit that the claimed invention is novel, non-obvious and enabled by the specification.

15. I declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

10th November 2008 — Date

Dr Matthew Rose